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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/566,697
Filing Date: May 10, 2006
Appellant(s): WANG ET AL.

Alex R. Sluzas
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/21/09 appealing from the Office action mailed 7/8/09.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

This appeal involves claims 2-4, 8-10, and 13-25.

Claims 1, 5-7 and 11-12 have been cancelled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct except the 35 USC 112, first

paragraph (new matter and written description) and 35 USC 112, second paragraph (in-part) rejections are withdrawn and therefore no longer an issue in the instant Appeal.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

7,026,443	SETTE	4-2006
6,602,510	FIKES	8-2003
6,291,214	RICHARDS	9-2001

Chengtao, Lin et al, Construction of malaria multivalent recombinant DNA vaccine with isocaudamer technique", Chinese Journal of Biochemistry and Molecular Biology, vol. 15, no.6, 1999, pages 974-977.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 (in-part)

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 20, the phrase "type" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "type"), thereby rendering the scope of the claim(s) unascertainable.

Claim Rejections - 35 USC § 102/103

Claims 2-3, 8-9 and 13-25 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chengtao, Lin et al (Chinese J. of Biochemistry, (1999), 15(6), 974-977)9hereinafter Lin).

Chengtao et al discloses throughout the article at e.g., the abstract:

> With the isocaudamers which have different recognition sequences and produce compatible cohesive ends, chimeric multi-epitope Plasmodium falciparum DNA vaccines including the multiplication of the single copy epitope and the tandem linkage of different kinds of epitopes were flexibly constructed. A specific B-cell response was detected by ELISA after the immunization of BALB/c mice with the chimeric antigen and demonstrated the usefulness of this strategy of constructing multi-epitope DNA vaccines.

Accordingly, the specific method steps of Lin using specific components anticipates or renders obvious the broad claimed method using broad components in the method.

See further the Response to Arguments below for the 103 rejection.

Claim Rejections - 35 USC § 103

Claims 2-3, 8-9 and 13-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sette et al (USP 7026443) or Fikes (USP 6602510) in view Richards et al (USP 6291214) or applicants' admission of known prior art.

Sette discloses in e.g., Example 10:

> A (method) procedure for the selection of peptide epitopes for vaccine compositions. The peptides in the composition can be in the form of a nucleic acid sequence, either single or one or more sequences (i.e., minigene) that encodes peptide(s), or can be single and/or polyepitopic peptides.
>
> When creating polyepitopic compositions, e.g. a minigene, it is typically desirable to generate the smallest peptide possible that encompasses the epitopes of interest.
>
> In cases where the sequences of multiple variants of the same target protein are available, potential peptide epitopes can also be selected on the basis of their conservancy. For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen.

In Example 11 Sette discloses:

> A minigene expression plasmid typically includes multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes. HLA class I supermotif or motif-bearing peptide epitopes derived from multiple HPV antigens, preferably including both early and late phase antigens, are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. The selected CTL and HTL

> epitopes are then incorporated into a minigene for expression in an expression vector.
>
> Overlapping oligonucleotides that can, for example, average about 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides. The final multiepitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR…….
>
> For example, a minigene can be prepared as follows. For a first PCR reaction, each of two oligonucleotides are annealed and extended: In an example using eight oligonucleotides, i.e., four pairs of primers, oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined…. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product. The full-length product is gel-purified and cloned into pCR-blunt and individual clones are screened by sequencing.

Fikes at e.g., throughout the patent at e.g., col. 30, line 35 discloses:

> …..A multi-epitope DNA plasmid encoding nine dominant HLA-A*0201- and A11-restricted CTL epitopes derived from the polymerase, envelope, and core proteins of HBV and human immunodeficiency virus (HIV), have been engineered. Immunization of HLA transgenic mice with this plasmid construct resulted in strong CTL induction responses against the nine CTL epitopes tested.
>
> For example, to create a DNA sequence encoding the selected epitopes (minigene) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated… These epitope-encoding DNA sequences may be

> directly adjoined, so that when translated, a continuous polypeptide sequence is created. However, to optimize expression and/or immunogenicity, additional elements can be incorporated into the minigene design such as spacer amino acid residues between epitopes.
>
> The minigene sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the minigene. Overlapping oligonucleotides (30-100 bases long) may be synthesized.. purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined. This synthetic minigene, encoding the epitope polypeptide, can then be cloned into a desired expression vector……
>
> ……Optimized peptide expression and immunogenicity can be achieved by certain modifications to a minigene construct……
>
> Once an expression vector is selected, the minigene is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate bacterial strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the minigene, as well as all other elements included in the vector, are confirmed using restriction mapping and DNA sequence analysis.….
>
> In vivo immunogenicity is a second approach for functional testing of minigene DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product…..Once again, lysis of target cells that were exposed to epitopes corresponding to those in the minigene, demonstrates DNA vaccine function and induction of CTLs.

Each of Sette and Fikes does not teach isocaudamer linkage.

Richards discloses throughout the patent at e.g., col. 25, lines 7-25:

> Both within and external to the lacZ.alpha. gene we have incorporated restriction enzyme sites needed for compatibility with commercial cDNA library synthesis

> methods. These include methods for either partial or random fragments. Most of these will not have the translation-initiation sites needed for protein expression. Therefore, it is desirable to have an efficient translation start site available on the cloning vector…….The restriction enzyme Esp3AI is an isocaudamer of EcoRI and so the pSK213 vector is compatible with EcoRI/XhoI-derived methods. This allows one to create one cDNA and clone it into the vector twice; once at the EcoRI site and including prokaryotic transcription, and a second time at the Esp3AI site and exclude transcription from occurring in E. coli.
>
> Applicants at page 10, line 5-6 disclose:
>
> ….Various isocaudamers are known in the art….

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use isocaudamer linkage in the method of either Sette or Fikes for the advantages taught by Richards above. Because of this known advantage one would be motivated to use said linkage. One would have a reasonable expectation of success in obtaining a polyepitopic chimera gene vaccine with an isocaudamer linkage since various isocaudamer has been known to have been successfully applied to various chimeric gene, as acknowledge by applicants and shown by Richards.

(10) Response to Argument

35 USC 112 Rejection

Appellant's brief indicates the Examiner has failed to provide any factual support for her assertion that "type" would

not be reasonably apprised by the scope of the invention by the use of this term which has long been used in U.S. patent practice and in fact appears in most patents.

In reply, each case is determined on its own merits/facts. Thus, while “type” appears in most patents however, the term as used in specification is vague and indefinite as read in the light of specification (published application (US 20070009892) definition:

> [0039] ...In addition, the criteria may include the immunological characteristics related to the antigen epitopes of interest, such as the specific **immunological types** and cytokines generated in the body elicited by the libraries tested or the cross protective effects elicited in animal models.

It is not clear from the above definition as to the type of immunological characteristics that are related to the antigen epitopes of interest are included or precluded by said term type. It is further vague and indefinite as to what aspects it is related to the antigen, especially when the antigen is only of interest. This is made more indefinite since the term “type” is coupled with the preceding phrase, “such as” (an all encompassing phrase). See MPEP § 2173.05(d). The Court also addressed this point head on in Ex parte Copenhaver stating, "The fact that the expression may have been used in claims of certain patents likewise does not alter our view on the question [i.e., that the use of the word **'type'** to an otherwise definite

expression extends the scope to render it objectionable under 35 U.S.C. § 112, second paragraph]." See Ex parte Copenhaver, 109 USPQ 118 (Bd. App. 1955).

35 USC 102(b)/103 Rejection

Appellants agree that while Chengtao discloses the use of isocaudamers having different recognition sequences to produce chimeric multi-epitope Plasmodium falciparum DNA vaccines however, argue that there is no disclosure of randomly assembling polyepitope chimeric genes with different lengths from the nucleic acid molecules encoding randomly combined bi-epitopes as is required by step (c) of each independent claim. Further, Lin does not disclose isolating polyepitope chimeric genes into a plurality of different length ranges, purifying and amplifying the isolated polyepitope chimeric genes, subcloning the purified and amplified polyepitope chimeric genes into expression vectors, or transforming prokaryotic hosts with the expression vectors to obtain polyepitope chimeric gene expression libraries, the expression libraries corresponding to different length ranges into which the polyepitope chimeric gene libraries were isolated. Further, Lin does not disclose assessing the diversity of the polyepitope chimeric genes in the expression libraries, and selecting at least one polyepitope

chimeric gene library based on diversity for use in preparing chimeric gene vaccines. In addition, Lin does not disclose immunizing animals with the polyepitope gene expression libraries to provide expression products of the polyepitope chimeric genes. Nor does Lin disclose detecting the immunogenicity of the expression products of the polyepitope chimeric genes. Lin does not disclose selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope chimeric gene expression libraries and the immunogenicity of the expression products of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries. Finally, Lin does not disclose screening the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines.

In reply, Lin discloses all the elements of the claim method using implicit terms for the claim term(s) e.g., random. For example, Lin teaches that with isocaudamer, having different recognition sequences with cohesive ends, tandem(bi-epitope) linking of different kinds of malaria epitopes are made. (i.e., the claim step(b), random combination of the different epitope by isocaudamer. (This is supported by the English Translation at e.g., Fig. 1 and paragraphs 2.1.2 and paragrah 2, Discussion

heading.) The isocaudamer linkage results in the multiplication of the single copy epitope (out of the multiple different length epitope derived from malaria antigen) and the tandem linkage of different kinds of epitopes. The tandem linkage of Lin is therefore random because the single copy of a fragment results in a library of multi-epitope clones of different length. Lin discloses that the polyepitope are derived from malaria antigen of different length fragments that result in different length sizes (ranges) as shown in the multiplication of a single clone. (The English translation supports this at e.g., paragraphs 2.1.1 -2.1.2.) Lin teaches the cloning and subcloning (reiterative screening of the different clones) that results in a final single polyepitope effective in immunizing mice (encompass the claim steps i-h.) (See paragraphs 2.1.2 and 2.2 of the English Translation copy. See the teachings in the English copy in its entirety.)

Appellants argue that nor does Lin render the presently claimed invention obvious. There is no teaching, suggestion or motivation in Lin to, inter alia, randomly assemble the nucleic acids molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths, nor to isolate the polyepitope chimeric genes into a plurality of different length ranges, nor to clone the polyepitope chimeric genes into expression vectors

to obtain polyepitope chimeric gene expression libraries, nor to assess the diversity of those libraries.

In reply, as stated above, the isocaudamer (i.e., different recognition sequences with compatible cohesive ends) would recognize or bind to the different clone fragments such that pool (library) of clones of different length is created. [Paragraph 1.2 of the English translation shows that the fragments are of different length. Bi-epitope combining the different length epitopes obviously produces different length epitopes, see paragraph 2.1.2.]. It would have been obvious to separate the different epitopes of different length into separate length ranges (sizes), as appellants recognize at page 10, lines 22-23, "one skilled in the art may set any desired length ranges." It would also be within the ordinary skill in the art to ascertain termination of the reiterative step of recloning(rescreening) of a pool(library) of epitopes when the desire immunogenicity of the polyepitope is obtained.

35 USC 103 Rejection

Appellants state that there is nothing in any of the individual references, nor in any combination of the individual references, which would teach, suggest, or motivate one of ordinary skill in the art to employ the presently claimed method. Appellants argue that Sette et al., who disclose

polyepitope gene vaccines for HPV, actually teach away from the presently claimed invention by the method disclosed in their apparently prophetic Example 11 for constructing minigene multi-epitope DNA plasmids. Sette et al. disclose plasmids including multiple CTL and HTL peptide epitopes, such as HLA-A2 supermotif-bearing epitopes, HLA-A1 motif-bearing epitopes, HLA DR supermotif- bearing epitopes et al. Sette et al. advises including epitopes derived from multiple viral antigens, in order to ensure broad population coverage. However, Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene. Thus, one of ordinary skill in the art would, following the disclosure of Sette et al., construct polyepitope chimeric gene vaccines with no attempt to randomize the sequence of epitopes within the construct, and without any recognition that the sequence could have an effect on the immunogenicity of the construct.

In reply, attention is drawn to the Sette reference which discloses at col. 35, lines 53-62, that the ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. Link or join is defined as any method known in the art for functionally connecting peptides, including, without limitation, recombinant fusion. (Sette at col.8, lines 52-56). Furthermore, Sette at e.g., col. 28, lines 56-60 discloses that

promoter sequences compatible with bacterial hosts are provided in plasmids containing convenient restriction sites (i.e., isocaudamer, as claim) for insertion of the desired coding sequence. The resulting expression vectors are transformed into suitable bacterial hosts. At Example 11, col. 60, lines 20-25, Sette teaches the preparation of minigene where each of two oligonucleotides are annealed and extended, in an example using eight oligonucleotides, i.e., four pairs of primers, oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined with a polymerase. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product. The full-length product is purified and cloned into pCR and individual clones are screened by sequencing. Sette discloses at e.g., cols. 63 up to col. 67, the immunogenecity of the construct at Examples 15-20.

The argued randomization of the sequence of epitopes within the construct is taught by Sette at e.g., Example 10:

> In cases where the sequences of **multiple variants** of the same target protein are available, potential peptide epitopes can also be selected on the basis of their conservancy. For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen.

Appellants argue that Fikes et al. discloses minigene vaccines incorporating multiple epitopes, but fails to disclose any recognition that the sequence of epitopes in the construct may have an effect on immunogenicity. Fikes et al. advises that optimized peptide expression and immunogenicity can be achieved by incorporating introns to facilitate efficient gene expression, and that expression can be increased mRNA stabilization sequences and sequences for replication in mammalian cells (co. 31, lines 35-42). However, Fikes et al. fail to disclose randomizing the sequence of epitopes in the construct and screening for optimized immunogenicity.

In response, please see the responses above under Sette since appellants merely present the same arguments as in the above. Appellants admit that the combination of Sette et al with Richards or the allegedly admitted prior art would at most teach or suggest the first two of the eight steps of independent claim 13 and the five steps of independent claim 23.

In reply, furthermore, the other steps of the claim method i.e., steps c-h of claim 13 are similarly taught by Sette above.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/TERESA WESSENDORF/

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